

MRS of Prostate Diseases
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According to the American Cancer Society, an estimated 234,460 new cases of prostate cancer (PCa) will occur and that there will be an estimated 27,350 deaths due to prostate cancer in the US during 2006 (1,2). The report also suggests that African American men are twice as vulnerable to prostate cancer compared to white men. Although the death rate has dropped over the last few years it still remains the second leading cause of cancer deaths among men after lung cancer in the United States. The ACS recommends that the PSA test and the digital rectal examination should be offered annually, beginning at age 50, to men who have a life expectancy of at least 10 years and those men that are at higher risk (African American men and those men with a strong family history of 1 or more first-degree relatives diagnosed with prostate cancer at an early age). The survival and successful treatment of PCa patients is dependent upon the early diagnosis of PCa. Further, the ability to monitor the progression and regression of malignancy is critical in the management of the disease. Currently the combination of digital rectal examination and prostate-specific antigen (PSA) testing is the primary diagnostic procedure. Typically, an elevated PSA or a nodule detected on physical examination prompts an evaluation and an eventual transrectal ultrasound-guided (TRUS) biopsy may reveal cancer. However in most cases, positive identification of PCa only becomes evident when malignancy has been established and the cancer has metastasized beyond the capsular region of the prostate. MRI in conjunction with endorectal coil provides superior visualization of zonal prostate anatomy compared to TRUS (3). MRI by itself can however be limited as various pathologies can mimic cancer thus compromising the diagnosis. In recent years, magnetic resonance spectroscopy of the prostate has shown to provide very useful metabolic information of the prostate. The combined use of MRI and MRSI has shown to increase the sensitivity and specificity in the detection of prostate cancer (4).

Citrate Metabolism

The metabolism of normal mammalian cells involves the complete oxidation of glucose and fat through the intermediary steps involving the synthesis and oxidation of citrate via the Krebs cycle (5). Coupled with phosphorylation, this intermediary synthesis and oxidation of citrate is essential for the cells to generate their major supply of cellular energy through the production of ATP. The citrate synthesized during this process in the Krebs cycle forms the source for acetyl-CoA required for lipogenesis. The Krebs cycle and the recycling of its intermediates are essential for the various reactions of amino acid metabolism. These established pathways are essential to normal mammalian aerobic cell metabolism, cellular function, survival, growth, and reproduction (6). The normal human prostate on the other hand does not go through the process of citrate oxidation thus accumulating large amounts of citrate which essentially is the end product of the intermediary metabolism. Cooper and Imfeld were the first to report that citrate levels were significantly decreased in prostate cancer tissue compared to the normal prostate or BPH (7). Shortly thereafter the same group suggested that the biochemical alterations seen through altered citrate metabolism may well occur before any malignant changes are histologically obvious (8). While these observations were made over four decades ago, it is only in the last decade that

scientists have been paying attention to the measurement of citrate levels within the prostate. The altered citrate metabolism has now been further studied by Costello, Franklin and their colleagues who have shed some light on the role of zinc in the production of citrate (9,10).

In addition to citrate, the normal and BPH prostate also accumulates high levels of zinc. The level of zinc in the normal prostate is about 150µg/g of tissue wet weight. However, the levels of zinc and citrate are not uniformly distributed throughout the prostate gland. For example in the normal peripheral zone there is high level of zinc concomitant with high levels of citrate. In the

Table 1	Citrate, nmole/g	Zinc µg/g
Normal (mixed tissue)	8,000	209
Normal (central zone)	4,000	-
Normal (peripheral zone)	13,000	-
BPH	8,000-15,000	589
PCa (mixed tissue)	1,000-2,000	55
PCa (malignant tissue)	500	-
Stromal tissue	150-300	-
Other soft tissue	150-450	30
Blood Plasma	90-110	1
Prostatic fluid	40,000-150,000	590

normal central gland, the levels of zinc and citrate are at a lower concentration (11). Table 1 lists the concentrations of citrate and zinc in different regions of the prostate in its different pathological condition. It is thought that in the presence of zinc, the mitochondrial aconitase activity that is responsible for citrate oxidation is severely limited in the normal prostate epithelial cells, which ultimately leads to the accumulation of citrate. The accumulation of citrate comes at the cost of ATP production which is reduced by about 65% in the normal prostate epithelial cells (14 moles of ATP) compared to other normal mammalian cells (38 moles of ATP) that completely oxidize glucose.

In prostate cancer however, the ability of intramitochondrial accumulation of zinc diminishes. It is thought that such a decrease in the zinc level restores the m-aconitase activity that leads to increased citrate oxidation. This is coupled with ATP production essential for progression towards malignancy (10,12,13). While many aspects of the zinc-citrate relationship are still under investigation, there is ample evidence suggesting that zinc-citrate interactions play an important role in the pathogenesis and progression of prostate malignancy.

Magnetic Resonance Imaging

Recent studies show that the combined use of an endorectal and phased-array coil and a high field strength MR imaging system provides the highest image resolution possible (3). MR imaging accurately depicts internal prostatic zonal anatomy and displays the physiologic complexity of the gland. Over the past several years, the superiority of MRI in the staging accuracy of cancer involving the peripheral zone has been consistently reported between 75% and 90 (4). Most prostate cancer involves the peripheral zone of the gland, where cancer is identified as low signal abnormality on T2-weighted imaging. Although MRI has allowed intra-prostatic evaluation of tumor location, results are often non-specific (14). Torricelli et al showed that cancer

could mimic post-biopsy hemorrhage, scar, prostatitis, or interglandular dysplasia on MR imaging of the prostate with specificity in the order of 50% (15).

Magnetic Resonance Spectroscopy

MRSI is a powerful tool that can provide useful biological information associated with many different metabolites (16). Proton (^1H) spectroscopy is attractive in terms of sensitivity, spatial resolution, signal to noise, and acquisition time. It has been widely used in the brain and its application and availability for imaging various anatomical regions of body has been increasing. MRS can provide a description of the chemical makeup of an imaged area in order to determine the presence of cancer (17). Molecules that can be studied with MRS include water, lipids, choline, citrate, lactate, creatine, and amino acids (16). Based on the initial work by Costello and Franklin at the University of Maryland, the prostate gland is unique in the body by the fact that it contains high levels of citrate (18). As the normal glandular epithelial cells are replaced by cancer, the concentration of citrate and choline change in the transformation to a malignant state. Choline levels increase and citrate levels decrease in the presence of active cancer (5). As mentioned above, the reason for the decline in the levels of citrate is the altered intermediate metabolism in the Krebs cycle (6). Although the mechanism for the elevation of the choline peaks is less understood, just as in the case of brain spectroscopy, its elevation is thought to be associated with changes in cell membrane synthesis and degradation that is normally associated with cancer. The choline resonance observed in-vivo at 3.22 ppm, sometimes referred to as total choline arises from the methyl hydrogens of trimethylamines and is comprised of choline, phosphocholine (PC), glycerophosphocholine (GPC), phosphoethanolamine (PE), glycerophosphoethanolamine (GPE), and ethanolamine (19-23). These compounds are essential in the synthesis and hydrolysis of phosphatidylcholine and phosphatidylethanolamines that are an integral part of the characteristic bilayer structure of cells and regulate membrane integrity and function. Polyamines such as spermine can be visualized in prostate MRSI (24). Polyamines are involved in many cellular processes such as maintenance of DNA structure, RNA processing, translation and protein activation (25,26). Disruption to the synthesis of polyamines is known to modulate the genetic effects of these genes. Polyamines can be visualized in proton MRSI as a broad peak between choline and creatine. Normal prostate epithelial cells will demonstrate large amounts of citrate and polyamines. The malignant cells on the other hand exhibit low levels of citrate and polyamines to the extent that the choline and creatine resonances are resolved to the baseline. One unfortunate consequence of prostate MRSI is the inability to monitor metabolites such as lactate and lipids in vivo due to the necessity for suppressing lipids to minimize contamination from the lipids surrounding the prostate gland. It has been shown in vitro that the citrate to lactate ratio can be used to discriminate prostate cancer from BPH and that the ratio can be used as an indicator of cancer aggressiveness (8). It is hoped that future MRSI improvements will allow for the interrogation of these metabolites.

MRSI Techniques

Although significant developments have been made with MRSI of the brain, the translation of this technology to other body parts including the prostate gland has proven to be far from trivial. In the case of the prostate gland, the deep location of the prostate, the possible movement of the prostate gland during the MRSI acquisition, and the dominating triglyceride signals from the

surrounding adipose tissues often pose a challenge in obtaining reliable quality spectra. Initial studies employing prostate spectroscopy used single voxel techniques such as STEAM (Stimulated Echo Acquisition Method) and PRESS (Point Resolved Spectroscopy) using the body coil (27-30). Usually the voxel size was large and encompassed both the peripheral zone and the central gland. Although these techniques showed the feasibility for performing proton spectroscopy, their use in the clinical setting was limited due to long scan times and the poor signal to noise of the spectra. However, with the arrival of 2D and 3D MRSI techniques the interest in prostate spectroscopy has increased (31-34). Several technical hurdles had to be overcome to reliably detect the resonances from the biological relevant compounds in the prostate including accurate localization and the suppression of large signals from both water and lipids (35-38).

3D-MRSI technique appears to be the most suitable for the prostate gland as it is able to provide the prostate metabolite level information with high spatial resolution for the entire gland. Typically PRESS localization and band selective excitation with gradient dephasing (BASING) for water and lipid suppression is used (35). 3D-MRSI provides an array of spectra from contiguous voxels from the entire prostate gland. The contiguous array of spectra that map the entire prostate are in alignment with the anatomical T1- and T2-weighted images allowing for a comparative interpretation between the anatomical images and the metabolic information. Investigators at the University of California San Francisco (UCSF) showed that 3D-MRSI can be used to differentiate and localize the tumor foci to a volume as small as 0.24cc (39-43). Similar results have been reported by the group in the University of Nijmegen, Netherlands who further refined the 3D-MRSI technique by using elliptical encoding to further reduce the scan time (44-46).

Interpretation resulting from a combined evaluation of the MR images and by metabolic changes observed through MRSI leads to the most confident identification of cancer with a specificity of up to 98% (42). Decreased signal intensity on T2-weighted images in conjunction with decreasing levels of citrate and polyamines and a concomitant increase in the levels of choline increases the specificity in the diagnosis of prostate cancer. Hence an increased choline to citrate ratio is usually used as a method for depicting prostate cancer. Since the choline and creatine resonances are inseparable for quantification purposes, most investigators use [Choline+Creatine]/Citrate (CC/C) for spectral analysis. A standardized scoring method was developed by Jung et al which is based on the deviation of the CC/C ratio from its normal value of 0.22 ± 0.013 . A voxel CC/C value within one standard deviation of this normal value was given a score of 1, a value between 1 and 2 standard deviations was given a score of 2, a value between 2 and 3 standard deviations was given a score of 3, a value between 3 and 4 standard deviations was given a score of 4, and a value greater than 4 standard deviations was assigned a score of 5. Additional adjustments were made to the score to account for the elevation of choline over creatine, reduced polyamines, and poor signal to noise ratios. In these ways each voxel obtained a score between 1 and 5 which was designated to an interpretative scale of likely benign, probably benign, equivocal, probably malignant and likely malignant corresponding to a voxel score from 1-5 respectively. Using this standardized five-point scale they were able to show good accuracy and excellent interobserver agreement. It should be noted that 3D-MRSI produces vast amounts of spectroscopic data and a standardized scale such as the one developed by Jung et al is likely to make the task of spectral interpretation less formidable (47). Such standardized scales will allow one to easily characterize the tumors aggressiveness and spatial extent.

The combination of MRI and MRSI in conjunction with the endorectal and phased-array body coil is emerging as the most sensitive tool for anatomic and metabolic evaluation of the prostate gland (4,48,49). Improvements in pulse sequences and MR technology have enabled the acquisition of the metabolic information from the entire prostate at high resolution within a reasonable time of ten minutes or less. Proton MRI/MRSI may be of great value for patients who are at increased risk for prostate cancer, for patients who have chosen watchful waiting, for longitudinal follow up from therapy, and in guiding various localized therapeutic treatments (50-52). MRI/MRSI of the prostate gland is likely to benefit from the recent trend towards ultra-high field magnet systems and emergence of multi-channel parallel imaging (53-55). Further newer techniques such as diffusion and perfusion are likely to increase the sensitivity and specificity of prostate cancer detection and characterization (56-64).

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